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Notes on 26-30 September Trip to Leukemia Project in Ukraine
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Introduction: This mini site-visit was arranged with Dr Margot Tirmarche to bring us up-to-date on the epidemiologic work of the project. I had also wanted to start a second draft of the 12 May 1998 "Consolidated Summary of Protocol Tasks for Leukemia Study" that Dr Finch and I had developed and on which we had comments in Dr Romanenko's letter of 19 July. Finally, I wanted to introduce a dialogue, at least with the epi group, and perhaps with Dr Romanenko, on the termination of Phase I and the transition to Phase II, if there was to be a Phase II. I met primarily with Dr Ledoschuk and Dr Gudzenko in their new office in Dr Cortushin's building, and with Dr Tsvetkova, and, briefly, with Dr Cortushin twice. With Dr Cortushin I discussed especially the technical aspects of selecting the cohort and Dr Howe's proposed workshop. There was also a short visit to Dr Romanenko. We met in his office and he had assembled, in addition to those already mentioned, Dr Dyagil, Dr Bazyka, and Dr Piatek. Unfortunately, Dr Tirmarche was grounded in Munich and was never able to make the trip.

Consolidated Summary of Protocol Tasks: I found Drs Ledoschuk and Gudzenko favorably disposed to the idea of the consolidated summary and able to make some positive suggestions for its revision. In addition we reviewed Dr Romanenko's July letter. Although we emphasized only those tasks that the epi group performs, or in which it participates, we also touched on several involving hematology and dosimetry, specifically:

Task 7, Identify High-Dose Sample (5.2.1.3). Epidemiology has not been reporting on this task, but it would be expected that its close association with the State Registry would enable it to make a contribution to the selection of high-dose cases. In fact, one would expect that all three groups, dosimetry, hematology, and epidemiology would contribute to the success of this task in different ways

Task 20, Update 1987-1997 Leukemia and Lymphoma (5.2.3.2). The hematologists had become concerned with diagnostic validity, which is relegated to Task 22 and need not be considered in this task.

Task 23, Learn Ascertainment, Other Diseases (5.2.3.4). This task also involved obtaining counts of the various diagnoses listed in the protocol (Appendix 1) and it was not anticipated that the hematological group would have to review diagnoses and classify cases. The thought expressed in the protocol was that a list of, say, myelofibrosis diagnoses would be made and taken to the Chernobyl Registry to see if they could be found there.This would seem to be a task for epidemiology, but perhaps the complexity of the task was not accurately visualized, for the hematology group has been reviewing case material and reporting on this task, not the epi group.

Task 29, Explore High-Dose Sample Size (5.2.4.2). In the protocol this is conceived as a statistical exercise to determine if the sample is large enough to have any power to carry out the investigations outlined in Chapter 4.3 of the protocol. Gathering high-dose cases was to be done in Task 7.

Phase I Document: We discussed the format and content of a final report on the results obtained in Phase I for each task, backed by the protocol and the 6 quarterly reports. The final report would be summary in nature and written to show clearly whether the questions raised in the protocol had been answered well enough to settle the issue of the operational feasibility of Phase II. After an introduction summarizing the development of the research protocol and the decision to perform a feasibility study as the basis for deciding whether to pursue a major scientific study, the document would present one task after another, citing first the questions raised in the protocol, and followed by the results achieved in that task. We tried this approach on Task 1, as follows:

Task 1: Investigate Registry (5.2.1.1)

The elements of the task

1. Develop a conceptual model of the State Registry of Ukraine with a description of the items of information needed for the database.

2. Determine the items of information in the individual files that will be needed for each member of the cohort (and subcohort) in the formation of the cohort (and subcohort) database

3. Explore the feasibility of the transfer of data from the Chernobyl Registry to the database for the project

Results Obtained

1. The State Registry was established in (year) in response to the USSR Ministry of Health Order # N. It was to record the results of the routine medical examinations of several classes of Chernobyl victims, including the cleanup workers, and to contain identifiers, demographic characteristics, and radiation dose. Eligibility for registration extends beyond the workers to evacuees, residents of "contaminated areas", and the children of these three groups. Registration was not automatic but required that the worker register at a medical facility, presenting his document of service as a cleanup worker. The Registry contains information on about 726,000 individuals. Dr Cortushin, Director of the Ukrainian Center of Informational Technologies and National Registry, and who has worked with the Registry since its inception, estimates that about 2/3 of the cleanup workers are in the Registry. In each oblast a central registry was established and its content transmitted to the UkrSSR Registry in Kiev, thence to the USSR Registry in Obninsk. The results of the medical examinations were made an integral part of the oblast registry, the registry of the UkrSSR (now the Republic of Ukraine), and formerly of the USSR registry in Obninsk. With the break-up of the USSR Ukraine determined to pursue the Registry program under the designation "Ukraine State Registry of Persons Suffered Following the Chernobyl Accident". It is operated by the Ministry of Health as a public health and research tool with the support of the Ministry of Ukraine for Questions on Extreme Situations and on Matters of Radiation Protection of the Population from the Effects of the Chernobyl Accident (formerly the Ministry of Chernobyl). There are no data known to the Center that compare the characteristics or the motivations of the 2/3 who registered and the 1/3 who did not. When the scientific protocol was developed the issue of registrants vs non-registrants was not raised and its investigation was not part of Phase I.

To create the database for Phase II the following types of information would be extracted from the Registry files: all identifiers, dates of service as a clean-up worker, any dosimetry information, all demographic and occupational (work) information, place and date of original

registration, residences of record, and hematologic diagnoses before and after the accident. Since the oblast of original registration will not update the file of a worker who has moved to another oblast and may have separated its files into "active" and "inactive" registrants, and since the oblast to which he moved may not have information on the original date and place of registration, the cohort will be selected from the national Registry in Kiev where his record would be complete.

2. Appendix 1 is a list of the items of information to be extracted from the Registry.

3. The feasibility of transferring information from the Registry to the database for Phase II has been successfully explored in the test oblast, Dniepropetrovskaya. The epidemiology group has been assured by Dr Cortushin that transfer from the National Registry will be similarly effective.

Epidemiology Offices: This was my first opportunity to see the new offices of the epidemiology group which now occupies a suite of three rooms on the 4th floor of Dr Cortushin's building. One large room is set up for 5-6 technical workers, each with a PC. Across the hall are two smaller rooms, one for Dr Ledoschuk, the other for Dr Gudzenko, both equipped with PCs. In addition, Dr Gudzenko's office has a FAX-telephone machine and a copier (not yet in operation). Dr Cortushin has more than two rooms on this floor in which NCI-provided equipment is visible. Both Dr Cortushin and Dr Gudzenko were having Computerland in for some finishing touches on the installation which includes a network. The furniture was new and modern. The overall impression was very positive.

Record Linkage Workshop: Asked about plans for the workshop I could only reply that: (1) the software Dr Howe had expected to be available would now cost $15K per installation; (2) he had decided to develop the necessary software with his own resources; and (3) in our last conversation with him he had indicated that he expected the workshop to take place early in December. When I learned that he had not been in touch with Dr Cortushin since the meeting in June I promised to urge him to do so on my return to the States. Dr Cortushin said he had 5 PCs he could provide, and with the 5 in the epidemiology group there would be room for 9 "students" to work in an interactive mode as Dr Howe plans. In addition, Dr Cortushin showed me a large room that would be suitable for the lectures and the location of the 5 PCs he could provide. We talked about the selection of the students and I suggested that there be three from Minsk representing the DCC there, the cancer registry, and the Chernobyl Registry. In Kiev the comparable organizations would be represented plus the leukemia project, 7 in all. Dr Cortushin will want at least two places for his staff, and Dr Howe's associate would also need one. Dr Cortushin and the leukemia epi group are looking forward to the workshop with great interest.

Evidence of Excess Leukemia among the Workers: When I asked Dr Gudzenko what data she had that might suggest a leukemogenic effect among the workers she responded that she had such data but had hesitated to publish since the cases had never been reviewed. Without negating the value of a diagnostic review I nevertheless urged her to consult Dr Howe about a collaborative effort to analyze and publish. I thought it would be a good task for the Columbia group and also I have some concern about the denominator she might use in calculating risk. If

she did not want to collaborate with the Columbia group I suggested that she work with Dr Prisyazhniuk who has a collaborative relationship with Dr Valerie Beral.

Payment for Bloods: Dr Finch had reported that the project was having considerable difficulty obtaining blood and was considering offering $10 per subject for expenses. We agreed that payment in Phase I would carry over to any Phase II operation, so that the expense for the subcohort was something to consider. I suggested that Dr Tsvetkova, an active participant in the discussions with Dr Finch, report her impressions informally to Dr Masnyk and that a letter be written for Dr Romanenko to send to Dr Masnyk raising this issue formally. On reflection overnight, however, it seemed to me that it would be better first to try harder, with more consideration of the appeals that could be made, and a more intensive follow-up, before adopting the payment scheme. The matter is, however, in their hands to do as they think best.

Meeting with Dr Romanenko: On 30 September we met Dr Romanenko in his office, with all those in attendance who are listed above in the introduction. For the most part I reported on the two days of discussion with Dr Ledoschuk and Dr Gudzenko, covering the reason why Dr Tirmarche had been unable to make the trip, our joint editing of some of the consolidated tasks, our approach to the final document to be used in deciding on Phase II, Dr Howe's workshop, and the new offices for epidemiology. In the discussion of the document I described as the basis for deciding about Phase II, Dr Romanenko asked for my appraisal of the chances for Phase II. I replied that I thought it would be approved handily only if, at the time of decision, there was external evidence of excess leukemia among the workers. In the absence of such data I thought the decision would rest on the possibility of making a contribution to the dose-rate effect as an explanation for the lack of a significant excess at 0.10 Gy. I said I didn't know if the study would have the power to make such a contribution. Dr Romanenko's opinion seemed similar to mine and I sensed a real doubt in his mind about the existence of an effect. Later I was told that Dr Bebeshko was convinced that there was none.

Having raised the issue with Dr Masnyk on the phone the day before, I broached the topic of extending the October visit to 2-3 days, noting that there was a lot of work to be done and that we ought to have some further discussion of the shape of the document to summarize what we will have learned in Phase I.

I also mentioned the developing plans for comparing the several dosimetric methods and I named the members of our respective groups who are developing a protocol to guide the comparison. I said I thought agreement would be reached soon and illustrated the technical nature of the planning by reference to the proposal that 10 of the 50 bloods we have planned for be obtained from "controls". This was to be discussed further, and although I happened to believe that it would be wasteful to draw blood from non-workers, it was something the group had to thrash out.

The Incomplete Registry: The incompleteness of the Registry is something to be better understood, perhaps, because one might think that the selection workers made whether to register may well have depended on their dose and their disease experience after serving in the Chernobyl clean-up tasks. On the other hand, there is no compulsion on us to strive for a cohort that is fully

representative of all cleanup workers. In fact, it would be to our advantage if the decision to register was dose-related and gave us a cohort with a somewhat higher dose disttribution. To be feared would be a correlation between dose and hematologic illness that influenced the likelihood of registration. That is, if high-dose individuals with hematologic illness were more likely to register than low-dose individuals with hematologic illness, there would be some distortion in any dose-response function. In our case, however, we plan to select individuals with minimal time between discharge from the Chernobyl workforce and registration although the interval has not yet been defined. It should be short enough to exclude the likelihood that hematologic illness could have developed in that interval, perhaps 18 or 24 months.

Incidental Intelligence: The grivna was down to 3.5 to the US dollar and lower on the street. Prices on local products had not moved, I was told, but those for imported goods were moving up sharply. Dr Derevyanko reported that the staff of her Institute had not received its government pay for 3 months and that the fall of the grivna just made matters worse. I believe I was told that salaries at Dr Romanenko's Center were about 6 weeks behind. Dr Romanenko emphasized the difficult position the Center would be in should Phase II not materialize.

Dr Contis (USAID project) has a representative in Kiev who called me and we tried to arrange a meeting with Dr Contis, who was also in the city, but we could not get our schedules to jibe.

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Attachment 1

Distribution
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